United States Department of Agriculture
Animal and Plant Health Inspection Service
Washington, D.C. 20250

March 19, 1998

VETERINARY SERVICES NOTICE 98-05

Subject: Ruminant Serum (RS) Import Requirements

To: Directors, VS Regions
Area Veterinarians in Charge, VS
Directors, Plant Protection and Quarantine (PPQ)
Ronald Caffey, PPQ

The purpose of this Notice is to provide detailed information on the U.S. Department of Agriculture (USDA), Animal and Plant Health Inspection Service (APHIS), requirements for the importation of RS. This information applies to the importation of all categories of RS, including fetal bovine serum, newborn and neonatal calf serum, calf serum, adult bovine serum, and goat/sheep serum. This Notice replaces the October 29, 1992, VS Notice on RS.

RS is commonly used in tissue culture media. A great deal of the RS used in the United States is imported, and a significant percentage of this imported serum is used for the production of livestock vaccines. Because of the potential livestock disease risks involved, the following USDA, APHIS, restrictions have been imposed on the importation of RS.

1. The importation of RS is prohibited from all countries not recognized by USDA as being free of foot-and-mouth disease (FMD) and bovine spongiform encephalopathy (BSE).

2. RS is not eligible for importation from any FMD- and BSE-free country unless it is authorized by a valid USDA permit. Applications for USDA permits will be reviewed on a case-by-case basis.

3. Imported RS is subject to either safety testing or gamma irradiation unless it originates from Canadian or New Zealand origin animals.

4. RS, with the exception of RS imported legally into Canada, must be imported <u>directly</u> from the country of origin. Any

exceptions to this policy will be addressed on a case-by-case basis.

5. The importation of RS, therefore, involves three activities*:

a. Submission of a completed VS Form 16-3, “Application for Permit to Import Controlled Material.” (Submit applications to USDA, APHIS, VS, National Center for Import-Export, Animal Products Program, 4700 River Road, Unit 40, Riverdale, Maryland, 20737-1231);

b. Collection of samples (as required by this Notice) by a VS Area Office representative; and

c. Sample verification by National Veterinary Services Laboratories, Ames, Iowa. (Sample collection and verification are not required for gamma irradiation.)

*Note: A user fee is assessed for each activity. (See Attachment No. 3, User Fees.)

USDA permits will not be issued authorizing RS imports unless the importer has made previous arrangements with USDA, APHIS, to comply with the restrictions delineated in this Notice. The importer must select either safety testing or gamma irradiation (except for countries discussed in item 3) to minimize the possibility for disease introduction by way of RS.

Each option is presented in Attachments Nos. 1 and 2, respectively, and subject to various procedures to prevent access to the RS during transport. These procedures are outlined in Attachment No. 4.

/s/
Joan M. Arnoldi
Deputy Administrator
Veterinary Services

Enclosures

OPTION NO. 1 -- SAFETY TESTING

Under this option, samples representative of all lots of imported ruminant serum (RS) would be collected by USDA, APHIS, personnel and submitted to the USDA, APHIS, National Veterinary Services Laboratories (NVSL), for safety testing. The specific tests performed would depend upon the country of origin. For example, RS from Mexico and Central America would be tested for exotic strains of bluetongue virus; Australian fetal bovine serum would be tested for Akabane and exotic bluetongue virus, whereas, adult RS would be tested for Akabane, exotic bluetongue virus, and bovine ephemeral fever. Five hundred milliliters (500 mL) of serum must be collected for each 500 liters in the shipment. (This equals one safety test.)

Safety testing and irradiation are subject to user fees. (See User Fees.)

Sample Collection:

Background

RS is shipped to the United States as either raw or finished product. Raw RS has not been aseptically filtered. It usually is shipped in plastic containers with a label identifying the product, the processing company, and lot number. Each container may have 2-4 liters of serum. Typically, 4-12 plastic containers are grouped and may be shipped in a large box. The RS is shipped frozen; this keeps endotoxins to a minimum and preserves the product.

Imported raw serum can be handled in one of three ways prior to resale: (1) kept in its original containers; (2) pooled and rebottled into a variety of container sizes (e.g., 2, 3.5, 4 liter) depending upon the client; or (3) pooled, filtered, and rebottled (100 mL, 500 mL, or 1,000 mL).

Finished RS has been aseptically filtered. It is shipped in vials (1 mL - 10 mL) or bottles (100 mL - 1,000 mL). Each container has a product label with the importing company’s name affixed to it. The product is ready for resale.

Procurement of samples

Sample collection for safety testing depends upon how the serum is shipped and handled once it reaches the quarantine location in the United States.

1. If the serum is pooled, 500 mL should be collected for every 500 liters pooled.

2. If the serum remains in its original containers (i.e., not pooled), 500 mL must be collected for every 500 liters shipped. Use the following 95 percent Confidence Table to determine the number of containers from which serum should be collected.

95 Percent Confidence Table	
Total Number Containers (any volume) in Shipment	Number Containers to be Sampled
20	19
50	34
100	44
150	48
200	51
250	52
300	53
350	54
400	54
450	55
500	55
600	56
700	56
800	56
1,000	56

Example: The shipment consists of 150 containers. Each container has 3.8 liters. Therefore, the total amount of serum in the shipment is 570 liters. A total of 1,000 mL would have to be collected and it would come from 48 containers. Approximately 21 mL (1,000 mL/48) would be collected from each of the 48 containers.

Testing:

Serological tests will be performed on sheep prior to inoculation with RS and 28 days after inoculation. The length of time required for performance of the safety test is approximately 5 weeks from the date the animals are inoculated. Should laboratory tests be positive, the consignment of imported RS must either be destroyed at the importer's expense or returned to the country of origin.

Approval of quarantine facilities:

All imported RS must remain under USDA quarantine at the USDA, APHIS-approved facility until the importer receives official notification that test results were negative.

In order to become a USDA, APHIS, facility approved to receive imported RS using the safety testing option, officials operating the facility must enter into a valid compliance agreement with USDA, APHIS. A copy of this compliance agreement is included in this Notice as Addendum No. 2. The agreement is valid for 2 years and must be renewed, with reinspection, when it expires.

If the quarantine storage during the safety testing is to be done at a facility already approved for this purpose, a written memorandum must be submitted from this USDA-approved facility stating that the imported serum will be handled according to the previously executed compliance agreement and the applicable permit restrictions will be followed.

The memorandum should be sent to the Animal Products Program staff.

OPTION NO. 2 -- GAMMA IRRADIATION

Under this option, all shipments of RS must be subjected to 3 megarads of gamma irradiation at a USDA, APHIS-approved irradiation facility in the United States.

In order for a U.S. irradiation facility to become approved by USDA, APHIS, for the purpose of irradiating imported RS, the facility must be inspected by a USDA, APHIS, representative. If the representative believes that the facility has adequate storage, sterilization, and recordkeeping capabilities, officials from the irradiation facility must complete a compliance agreement. (See Addendum No. 3.) The agreement is valid for 2 years.

In order to maintain approval, operators of the irradiation facility must fully comply with all restrictions in the agreement and renew the agreement, through reinspection, every 2 years.

Shipments of irradiated RS may be released to the U.S. importer after the entire shipment has received the required minimum treatment of 3 megarads.

Both the irradiation facility and the U.S. importer are required to keep on file, for a minimum of 2 years, copies of irradiation certificates and to make these certificates available to APHIS inspectors during routine inspections.

USER FEES

Permit application, inspection of the quarantine or irradiation facility, safety testing, and gamma irradiation are subject to user fees. Payment arrangements may be made by contacting the Animal Products Program staff.

*Schedule of Fees

The fees associated with processing permit applications are as follows:

Service	Fee
Original Application (No facility inspection required)	$27.50
Application with Facility Inspection Required	$208.50
Application for Renewal	$15.00
Amended Application	$11.50
Sample Collection for Safety Testing	At Hourly Rate
One Safety Test	$660.00

*Note: User fees are subject to change. Please check with the Animal Products Program staff to obtain the most current information regarding user fees.

PROCEDURES FOR MONITORING TRANSPORT OF RUMINANT SERUM (RS) IMPORTED UNDER USDA PERMIT WITH REQUIREMENT FOR EITHER IRRADIATION OR SAFETY TESTING

The USDA permit will indicate if the RS is to be irradiated or safety tested. Regardless of the option selected, the following procedures are to be followed:

1. APHIS port personnel shall carefully review all permit restrictions and make certain that all incoming shipping documents required by the permit are present.

2. Shipping containers must have seals from the country of origin applied in a manner which makes them tamper proof. Some examples of acceptable seals are: (1) plastic shrink wrap; (2) plastic or metal tyden type seals; or (3) plastic, metal, or polyester/fiberglass filament-reinforced bands around the circumferences.

3. Seals from the country of origin must be on the shipping containers and intact upon arrival at the U.S. port of arrival. Containers which are not sealed or whose seals are not intact must be returned to the country of origin. Shipping costs will be paid by the importer.

4. The consignment must be delivered directly to the facility specified on the permit. A VS Form 16-78 shall be completed at the port of arrival and copies distributed to the Area Veterinarian in Charge (AVIC) in the State of destination. Temporary storage may be used if: (1) the permit authorizes temporary holding at a USDA, APHIS-approved intermediate holding facility, or (2) a connecting flight is delayed or canceled. Arrangements must be made in advance with APHIS port personnel if the consignment must be stored at an airline’s storage area. Seals from the country of origin must be intact upon arrival at the temporary storage facility and must remain intact until the consignment is delivered to the approved processing facility.

When the shipment arrives at the destination specified on the permit, a representative designated by the firm (manager of quality assurance or designee) will record the date of arrival and verify that the seals from the country of origin are still intact. Within 3 working days, the U.S. importer (or representative from the irradiation facility or quarantine facility) shall notify the AVIC in the destination State of the shipment’s arrival.

APHIS-approved facilities are required to isolate the quarantined RS until it has been irradiated or safety tested. During the quarantine period, there shall be no unauthorized access to the imported material. Quarantined material shall be held in an area clearly demarcated with a sign stating "Restricted Material Under Quarantine by the USDA, APHIS."

USDA, APHIS, field personnel shall monitor records once a year to ensure that the importer, approved quarantine facility, or irradiation facility is complying with all restrictions delineated in the compliance agreements. (See Addendum No. 2 or 3.)

Addendum No. 1

TAMPER-PROOFING OF SAMPLES

Tamper-proofing involves placing samples in cartons and subsequently sealing the cartons so they cannot be opened or the contents disturbed without it being obvious to NVSL upon receipt.

Samples are to be packaged to withstand leakage of contents, shocks, pressure changes, and other conditions incident to ordinary handling in transportation. Special care should be taken to prevent breakage of glass containers. All vials, glass or plastic, should be packed in nested cartons or packed by some other method commonly used when shipping samples to distributors or consumers.

The shipping container should be secured using either a polyester filament-reinforced or fiberglass filament-reinforced tape applied around the circumferences. Alternative methods of securing the container are permissible provided they are tamper proof.

Remember that leakage of liquid from a carton may mean refusal by a common carrier to handle it, and damaged shipments may be destroyed by NVSL personnel upon receipt.

Return filled tamper proof shipping cartons to the U.S. importer, as the importer is responsible for the actual shipment of samples to NVSL. The correct address for samples is: USDA, APHIS, NVSL, 13th and Dayton Road, Ames, IA 50010. Samples should be sent early in the workweek. Never send samples the day before a Government holiday or on Fridays.

Addendum No. 2
(to be executed by the AVIC)

COMPLIANCE AGREEMENT

BETWEEN

(NAME AND ADDRESS OF U.S. IMPORTER/QUARANTINE FACILITY OF RUMINANT SERUM)

AND

UNITED STATES DEPARTMENT OF AGRICULTURE (USDA)
ANIMAL AND PLANT HEALTH INSPECTION SERVICE (APHIS)
VETERINARY SERVICES (VS)

This is to certify that

_____will:
(Name and address of U.S. importer or quarantine facility)

1. Receive and store restricted, imported ruminant serum (RS) only in the USDA, APHIS-approved facility designated above.

2. Notify the USDA, APHIS, Area Veterinarian in Charge (AVIC) (in the State where USDA, APHIS-approved facility is located), within 3 working days of the arrival of a shipment of imported serum at the facility. The importer/quarantine facility shall inform the AVIC of the following:

a. USDA permit number authorizing the importation;

b. Country of origin;

c. Quantity of material that has arrived in the consignment; and

d. The date, if known, when an APHIS representative can collect samples for submission to the USDA, National Veterinary Services Laboratories, for safety testing. If the date for sample collection is not known, scheduling for the collection shall be made with the APHIS representative.

3. Store all imported RS being held, pending negative laboratory test results, separate from nonrestricted RS and clearly mark the restricted product with a sign stating “Restricted Material Under Quarantine by the U.S. Department of Agriculture, Animal and Plant Health Inspection Service. Distribution of Product Prohibited.”

4. Maintain a complete inventory of each shipment of RS, including the date of importation, number of containers, amount of serum per container, and the lot and batch number(s). This inventory log shall be up to date and made available to USDA, APHIS, personnel during routine inspections. Inventory records, along with official certificates of origin for each imported shipment of RS, shall be kept on file at the importer's/quarantine facility’s establishment for a minimum of 2 years.

5. Maintain records of imported RS, which is filtered and rebottled prior to the collection of samples for safety testing, indicating the date of filtration (i.e., the production date) and the lot numbers of the material pooled.

6. Maintain labels on all bottles of imported, restricted RS (regardless of whether it remains in original containers in which material was imported or is filtered and placed in retail-sized bottles for distribution) to allow for complete traceability of product to the country of origin. If new lot numbers are assigned following pooling, filtration, and final bottling, records must be kept that clearly show which imported lots were utilized for the final production lot.

7. Implement procedures to ensure that no product is distributed until authorized by USDA, APHIS. Authorization will be granted upon receipt of written laboratory confirmation that samples from the lot(s) in quarantine were negative for viruses exotic to the United States.

8. Under USDA supervision, agree to have the product destroyed or returned to the country of origin if the restricted RS tests positively for viruses exotic to the United States. All costs for destruction or re-exportation of the product shall be borne by the U.S. importer.

9. Allow USDA, APHIS, inspectors to make unannounced inspections (during regular business hours) to monitor compliance with this agreement and to provide USDA, APHIS, inspectors with the records and certificates described in this Notice. If the USDA, APHIS, inspector determines that

_____

(Name and address of U.S. importer or quarantine facility)

has failed to comply with this agreement, approval from USDA, APHIS, will be canceled and permits authorizing the importer to import RS will be revoked. Any appeals for cancellation must be directed to the Deputy Administrator, USDA, APHIS, VS, within 10 days after receiving written notification of the cancellation.

_____ _____

Date Signature
Owner/Operator

_____ _____

Date Signature
USDA, APHIS, VS
Area Veterinarian in Charge

_____

Expiration Date

Addendum No. 3
(executed by AVIC)

COMPLIANCE AGREEMENT

BETWEEN

(NAME AND ADDRESS OF U.S. IRRADIATION FACILITY)

AND

UNITED STATES DEPARTMENT OF AGRICULTURE (USDA)
ANIMAL AND PLANT HEALTH INSPECTION SERVICE (APHIS)
VETERINARY SERVICES (VS)

This is to certify that

_____ will:
(Name and address of irradiation facility)

1. Receive and store restricted, imported ruminant serum (RS) only in the USDA, APHIS-approved facility designated above.

2. Notify the USDA, APHIS, Area Veterinarian in Charge (AVIC) (in the State where the USDA, APHIS-approved irradiation facility is located), within 3 working days of the arrival of a shipment of imported RS at the facility. An official from the irradiation facility shall inform the AVIC of the following:

a. USDA permit number authorizing the importation;

b. Country of origin;

c. Quantity of material that has arrived in the consignment; and

d. Date when product has been scheduled for irradiation treatment.

3. Store all imported RS awaiting irradiation on the nonsterile side of the plant until it has been sent through the sterilizer.

4. Insert a radiochromic dye file into each lot of RS entering the sterilizer. Each dosimeter shall be placed in the low-dose zone to ensure all products receive at least 3 megarads (30 KGy).

5. Not release the irradiated product to the U.S. importer until each dosimeter has been examined and a certificate has been issued certifying that the lot of RS has received a minimum dose of 3 megarads (30 KGy).

6. Maintain a copy of the irradiation certificates for imported RS on file at the irradiation facility for a minimum of 2 years and make available to USDA, APHIS, inspectors copies of certificates during routine inspections.

7. Allow USDA, APHIS, inspectors to make unannounced inspections (during regular business hours) to monitor compliance with this agreement and to provide USDA, APHIS, inspectors with the records and certificates described in this notice. If the USDA, APHIS, inspector determines that

_____
(Name and address of irradiation facility)

has failed to comply with this agreement, approval from USDA, APHIS, to receive and store restricted, imported RS will be canceled. Any appeals for cancellation must be directed to the Deputy Administrator, USDA, APHIS, VS, within 10 days after receiving written notification of the cancellation.

Date	Signature Owner/Operator
Date	Signature USDA, APHIS, VS Area Veterinarian in Charge

Expiration Date